Spectrum of HNF1A Somatic Mutations in Hepatocellular Adenoma Differs From That in Patients With MODY3 and Suggests Genotoxic Damage

Titre	Spectrum of HNF1A Somatic Mutations in Hepatocellular Adenoma Differs From That in Patients With MODY3 and Suggests Genotoxic Damage
Type de publication	Article de revue
Auteur	Jeannot, E. [1], Mellottee, L. [2], Bioulac-Sage, Paulette [3], Balabaud, Charles [4], Scoazec, Jean-Yves [5], Tran Van Nhieu, Jeanne [6], Bacq, Yannick [7], Michalak, Sophie [8], Buob, D. [9], Laurent-Puig, Pierre [10], Rusyn, I. [11], Zucman-Rossi, Jessica [12]
Organisme	Groupe d'etude Genetique des Tumeurs Hepatiques (INSERM Network) [13]
Pays	Etats-Unis
Editeur	American Diabetes Association
Ville	New York
Type	Article scientifique dans une revue à comité de lecture
Année	2010
Langue	Anglais
Date	Jan-07-2010
Numéro	7
Pagination	1836-44
Volume	59
Titre de la revue	Diabetes
ISSN	0012-1797

Résumé en anglais	OBJECTIVE Maturity onset diabetes of the young type 3 (MODY3) is a consequence of heterozygous germline mutation in HNF1A. A subtype of hepatocellular adenoma (HCA) is also caused by biallelic somatic HNF1A mutations (H-HCA), and rare HCA may be related to MODY3. To better understand a relationship between the development of MODY3 and HCA, we compared both germline and somatic spectra of HNF1A mutations. RESEARCH DESIGN AND METHODS We compared 151 somatic HNF1A mutations in HCA with 364 germline mutations described in MODY3. We searched for genotoxic and oxidative stress features in HCA and surrounding liver tissue. RESULTS A spectrum of HNF1A somatic mutations significantly differed from the germline changes in MODY3. In HCA, we identified a specific hot spot at codon 206, nonsense and frameshift mutations mainly in the NH2-terminal part, and almost all amino acid substitutions were restricted to the POU-H domain. The high frequency of G-to-T tranversions, predominantly found on the nontranscribed DNA strand, suggested a genotoxic mechanism. However, no features of oxidative stress were observed in the nontumor liver tissue. Finally, in a few MODY3 patients with HNF1A germline mutation leading to amino acid substitutions outside the POU-H domain, we identified a different subtype of HCA either with a gp130 and/or CTNNB1 activating mutation. CONCLUSIONS Germline HNF1A mutations could be associated with different molecular subtypes of HCA. H-HCA showed mutations profoundly inactivating hepatocyte nuclear factor-1α function; they are associated with a genotoxic signature suggesting a specific toxicant exposure that could be associated with genetic predisposition.
URL de la notice	http://okina.univ-angers.fr/publications/ua12876 [14]
DOI	10.2337/db09-1819 [15]
Titre abrégé	Diabetes

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